REMARKS

Claim 90 has been amended to include the element from previous claim 95, which has been cancelled as redundant. Claim 90 has also been amended to clarify that the monitoring results from a series of measurements, as recited at *e.g.*, p. 34, lines 13-15. No amendment should be construed as an acquiescence in any ground of rejection. Applicants address the Examiner's comments using the paragraph numbering of the office action.

¶5. The Examiner has withdrawn the species election requirement based on applicants' traversal filed October 4, 2004 and stated "claims 50, 69, 70 and 73-100 are under examination." Claims 50 and 69-70 were canceled by entry of the amendment filed March 14, 2005. Thus, claims 90-94, 96-98 and 100 are now under examination. Applicants note that the withdrawal of the election requirement is untimely as the claims are no longer pending. Applicants seek further clarification as to what is meant by the timing of the withdrawal of the species election requirement.

¶7. The Examiner is referred to paragraph number 7 of applicants' previous response.

¶¶8-9. Claims 90-92, 96-97 and 99 are rejected as allegedly anticipated by Solomon, WO 99/60024. Solomon is alleged to teach *in vivo* and *in vitro* methods of amyloid removal with anti-amyloid antibodies that enhance the cell-mediated response to deposits of amyloid. In particular, the Examiner alleges that Figures 2A and 2B show *in vitro* adherence of human neutrophils after amyloid plaques were treated with anti-human immunoglobulin light chain (IgLC) monoclonal antibodies.

Applicants maintain traverse for the reasons given in the previous response. However, the rejection is moot in view of the incorporation of the element from claim 95 into claim 90. Claim 99 has been canceled thus further mooting the rejection with regard to claim 99. Claim 95 was not subject to the rejection.

¶10. Claims 90-98 and 100 stand rejected as allegedly anticipated by Vitek as further evidenced by Benjamini. Vitek is alleged to teach that an AGE-bearing targeting agent can be tested for efficacy *in vitro* or *in vivo* (citing to the paragraph spanning columns 21 and 22, column 22, line 54 to column 23, line 4 and column 24, lines 13-25). The Examiner cites column 32, Example 2 as allegedly disclosing that *in vitro* analysis may be performed in tissue sections viewed and fixed *in vitro*. The Examiner cites Benjamini as allegedly teaching that ADCC assays are widely accepted in the art, and include cytolysis mediated via antigen/antibody binding. The Examiner relies on Vitek's discussion of polyclonal antibodies for an antibody binding to an epitope within Aβ1-7. This rejection is respectfully traversed.

The Examiner's comments regarding Vitek in the present office action are substantially similar to those in previous office actions; however, as in previous office action, the Examiner has not fully addressed distinctions pointed out by applicants. Specifically, applicants pointed out that Vitek's method differs from that claimed in at least two respects: (1) Vitek does not disclose simultaneous presence of an antibody and phagocytic cells in an *in vitro* clearing reaction; and, (2) nor does it disclose that the clearing reaction screens an antibody for clearing activity. Although Vitek discusses various methods of treatment and diagnosis, only a small portion of the patent relates to an *in vitro* assay for phagocytosis at col. 22, lines 54-66. As discussed in the last response and reiterated below, the assay discussed at col. 22, lines 54-66 is not the same as that claimed. In Vitek's *in vitro* assay, the object is not to screen an antibody but rather to screen AGE-TF (thioflavin) for capacity to modify insoluble or aggregated Aβ (col. 22, lines 53-55). This is achieved by the following steps. First, AGE-TF is contacted with aggregated Aβ. The incorporation of AGE-TF into aggregated Aβ is then tested by ELISA using an antibody (col. 22, lines 58-61). The antibody in this step is used simply as a conventional diagnostic reagent, and is not itself being screened for anything. After verifying incorporation of AGE-TF, phagocytic cells are added to test for clearance of AGE-TF modified Aβ (col. 22, lines 61-65). However, at the time the phagocytic cells are added, there is no indication that the antibody used for the ELISA is still present. It would be most logical and typical practice when performing a diagnostic step on an intermediate product in a process to perform the diagnostic

step on only a sample of the intermediate so as to avoid influencing the further processing of the intermediate by contamination with the reagents in the diagnostic step. In any event, insofar as there is doubt as to whether Vitek proposes adding phagocytic cells to the same or a different vessel to that in which the ELISA using antibody to AGE-TF is performed, that doubt should inure to the benefit of applicants given that the burden of proof rests on the PTO (*In re Piasecki*, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-88 (Fed. Cir. 1984)).

The paragraph spanning cols. 22 and 23 of Vitek discuss a binding assay not a clearing assay (*see* col. 22, line 67). Moreover, the paragraph refers to "[i]nvolvement of *AGE-receptor-mediated* uptake by phagocytic cells" (col. 22, line 66-67, emphasis supplied) suggesting that phagocytic cells bind to AGE-receptors, rather than antibody Fc domains. Such is also consistent with the excerpt from Vitek quoted above.

Column 24, lines 13-25 of Vitek refers to "detecting the amount of amyloid in affected tissues, and comparing that amount to the amount in control animals..." The references to "affected tissues" and "control animals" suggest an *in vivo* assay, not an assay in which an amyloid deposit is combined with an antibody and phagocytic cells *in vitro*, as claimed.

Column 32, example 2 of Vitek reports staining of tissue sections from an infected hamster brain with antisera to prion protein and to AGE to show co-localization of the two sera. The assay used antibodies for detection, and not to screen them for clearing activity in the presence of phagocytic cells. Thus, none of the sections of Vitek cited by the Examiner discloses or suggests a method of screening an antibody as claimed.

Although not expressly stated, the Examiner's reliance on Benjamini appears to be based on a theory of inherency. However, "[i]nherency ... *may not be established by probabilities or possibilities" Mehl/Biophile v. Milgraum,* 52 USPQ2d 1303, 1305 (Fed. Cir. 1999) (emphasis supplied). "The mere fact that a certain thing *may* result from a given set of circumstances *is not sufficient* to establish inherency." *In re Rijckaert*, 28 USPQ2d 1955 (Fed. Cir. 1993) (emphasis supplied). Here, as discussed at length above and in previous responses, Vitek discusses a clearing assay involving AGE-modified Aβ and phagocytic cells but does not say that an antibody is present. Benjamini indicates that one possible mechanism of phagocytic

cells is to bind to receptors present on antibodies, but does not say that this is the only mechanism. Paul, *Immunology* (3rd Ed., Raven Press, 1993) at p. 942, second column, second paragraph indicates that as of 1993 phagocytic cells were known to recognize at least forty other kinds of receptor. As noted above, Vitek refers to "[i]nvolvement of *AGE-receptor-mediated* uptake by phagocytic cells" (col. 22, line 66-67, emphasis supplied) suggesting a mechanism in which phagocytic cells bind to AGE-receptors not antibodies. Given the number of receptors on phagocytic cells and Vitek's comments regarding phagocytic cell uptake being mediated by AGE-receptors, it cannot be concluded that antibodies must necessarily be present in Vitek's assay.

As noted, the present office action does not comment on the above remarks but instead cites to some additional sections of Vitek. These citations differ from those in the previous office action and will be addressed in turn. The Examiner cites to column 6, line 36 to column 7, line 15 as discussing a role of phagocytic cells and that a particular embodiment of the invention involves administering an antibody to AGE-amyloid. However, the cited discussion is of *in vivo* methods of therapy. The role of phagocytosis, if any, in *in vivo* therapy is irrelevant to the distinctions between Vitek's *in vitro* assay and that claimed, as discussed above. Moreover, the cited passage indicates that it is AGE-amyloid per se, not antibodies to it that act via a phagocytic mechanism.

> The presence of high levels of AGE-amyloid polypeptides in amyloidogenic diseases indicates that the normal clearance mechanisms for such polypeptides are faulty. Therefore, in a further aspect, the present invention provides compositions and methods for stimulating or inducing mechanisms of recognition and removal of AGE-amyloid in an animal, i.e., the invention contemplates activation of the scavenger system in an animal's body to remove the amyloid plaques. Such scavenger systems include the activity of phagocytic cells, e.g., macrophages and, in neural tissue, microglial cells.
>
> Accordingly, the invention provides for stimulating or activating the natural scavenger systems by administration of stimulatory agents, including but not limited to, an advanced glycosylation endproduct, an AGE bound to a carrier, the fluorescent

> chromophore 2-(2-furoyl)-4(5)-(2-furanyl)-1H-imidazole (FFI) bound to a carrier, a monokine (e.g., lymphokine or cytokine) that stimulates phagocytic cells in the animal to increase the activity of recognizing and removing AGE-amyloid, and mixtures thereof. In a specific aspect, the AGE is an AGE-amyloid polypeptide.
>
> *See* Col. 6, line 36 to col. 6, line 63.

The discussion of antibodies at col. 7, lines 11-15 occurs three paragraphs later and is not specifically associated with a phagocytic mechanism.

The Examiner next cites to col. 15, lines 8-26 as discussing "selection or screening of particular antibodies that comprise the removal/opsonizing/neutralizing effect mediated by phagocytes/macrophages/microgilia." Applicants do not find such teaching at col. 15, lines 8-26. The passage is reproduced below:

> In another embodiment, inhibitors of AGE can be antibodies. Antibodies can bind to and inactivate or mediate clearance of AGE-modified amyloid polypeptides. In one aspect of the invention, the antibody described in Makita et al. (1992, J. Biol. Chem. 267:5133-38) can be used. The invention further provides for generation of antibodies to AGE epitopes of AGE-amyloid polypeptides. Such antibodies can be prepared using techniques well known in the art. Preferably, the inmmunogen used to prepare the antibodies is an AGE-amyloid protein. In a specific aspect, AGE-βAP can be used. In another embodiment, AGE-amylin can be used.
>
> The AGE-βAP or AGE-amylin may be used to produce antibody(ies) to themselves. Such antibodies can be produced and isolated by standard methods including the well known hybridoma techniques. Generally, antibodies can be produced by immunization of an animal with AGE-βAP or AGE-amylin, free or conjugated with a carrier protein, such as but not limited to keyhole limpet hemocyanin (KLH) or BSA, preferably admixed with an adjuvant as defined above.
>
> *See* Vitek at col. 15, lines 8-26

The cited passage says nothing about a "removal/opsonizing/neutralizing effect" and nothing about screening antibodies other than by the use of "well-known hybridoma techniques."

Finally, the Examiner cites to columns 16-24 as teaching "treatment of amyloidosis by increasing AGE clearance." Columns 22-24 of this excerpt have been extensively discussed above. The remainder discusses *in vivo* methods of treatment using AGE-amyloid. This discussion is not relevant to the differences between Vitek's *in vitro* assay and the claimed assay noted above.

¶¶11-12. Claims 90-98 and 100 stand rejected as obvious over Vitek as further evidenced by Benjamini, Solomon WO 99/60024, Herlyn, Jarling, Bellotti and Jorbeck. Vitek is cited as above. The Examiner acknowledges that Vitek does not teach methods in which an antibody binding within Aβ1-7 is administered to a sample from Alzheimer's patient. Benjamini, Solomon, Herlyn, Jarling, Bellotti and Jorbeck are cited as allegedly teaching that one of skill in the art is highly versed in assessing the ability of any antibody to mediate clearance of an antigen or cell via phagocytosis or cytolysis. The Examiner alleges that one would have been motivated to assess such activity *in vitro* given the successful teachings of the AGE-beta amyloid antibody *in vivo* as taught by Vitek. In response to applicants' request for clarification as to what the secondary references are being relied on for the Examiner alleges that the "multiple references are cumulative to the widely art accepted principles and assays directed to assessing clearing activity of antibodies in presence of noted antigenic samples, be they from *in vitro* or *in vitro* derived protocols." This rejection is respectfully traversed insofar as applied to the pending claims.

In applicants' view, all of the pending claims differ from Vitek in requiring a step of combining an amyloid deposit of Aβ, an antibody to be screened and phagoyctic cells *in vitro*. Vitek only discusses combining AGE-modified Aβ and phagocytic cells *in vitro*, and proposes a theory whereby the phagocytic cells bind to AGE receptors. Vitek's discussion of an antibody to AGE-Aβ *in vivo* would not have suggested modification of the *in vitro* assay because, among other reasons, Vitek did not show success of the antibody *in vivo*, or that it operated by a phagocytic mechanism *in vivo*.

Insofar as the rejection can be understood, applicants understand the Examiner to be saying that if *arguendo* applicants are correct that Vitek does not disclose using an antibody in his *in vitro* assay, then it would have been obvious to add one anyway because of alleged

"widely art accepted principles and assays directed to assessing clearing activity of antibodies." However, if this is the Examiner's position, it does not take into account that Vitek says nothing about screening antibodies in his *in vitro* assay. An antibody is only mentioned as agent for an ELISA assay. The relevance of allegedly widely accepted principles for screening antibodies would not be apparent to the use of an antibody in an ELISA. Further, this position also assumes that the skilled person would think that Vitek must be wrong or at least not have clearly expressed himself when he refers to "[i]nvolvement of *AGE-receptor-mediated* uptake by phagocytic cells" (col. 22, line 66-67, emphasis supplied). The lack of mention of any antibody bridging AGE-receptors and phagocytic cells suggests Vitek contemplated that phagocytic cells bind to AGE-amyloid receptors directly. Such is also consistent with Vitek's object of stimulating "phagocytic cells in the animal to increase the activity of *recognizing* and removing AGE-amyloid" (emphasis supplied) (col. 6, lines 53-55). Moreover, as discussed in the previous response, none of the secondary references concerns *in vitro* assays for phagocytosis of amyloid deposits of Aβ. For example, Belloti discusses assays on B-cells, Jarling discuses assays on alphaviruses, Herlyn discusses assays on various cancer cells, Solomon discusses a binding assay on deposits of human IgLC, Jorbeck discusses assays on PEC exudates, and Benjamini is a textbook generally discussing mechanisms of antibodies and phagocytic cells.

Because of Vitek's lack of disclosure of screening antibodies by an *in vitro* phagocytic assay, and failure to indicate that antibodies act via a phagocytic mechanism at all, it is respectfully submitted that the skilled person would not have been motivated to modify Vitek's assay by incorporating elements from other assays conducted in contexts not involving Aβ.

Insofar as the rejection is directed against claims 93, 98 and 100, the claims are further distinguished from Vitek in that Vitek does not disclose performing an *in vitro* assay on an amyloid deposit from an Alzheimer's patient or an animal model with Alzheimer's pathology, nor a monoclonal antibody binding within residues 1-7 of Aβ. The Examiner appears to acknowledge these deficiencies, but has not identified any compensatory teaching in the secondary references. Accordingly, claims 93, 98 and 100 are distinguished on additional grounds.

¶13. Claim 90-98 and 100 stand rejected over Vitek as further evidenced by Benjamini, Solomon et al. WO 99/60024, Solomon US 5,688,651, Frenkel, Herelyn, Jarling, Bellotti, and Jorbeck. The '651 patent is alleged to provide for solubilization of amyloid aggregates preventing further aggregation. Frenkel is alleged to definitively establish the epitope specificity of monoclonal antibodies possessing anti-aggregating properties. This rejection is respectfully traversed.

Applicants initially note that the rejection is unclear in citing nine references but not indicating which references are primary, second and tertiary etc, and which if any of the references are cited in the alternative. In the absence of such information, it is difficult to assess what it being combined with what or what is alleged to have motivated the combination.

Insofar as the rejection can be understood, applicants understand the Examiner to be citing Frenkel as providing evidence of an epitope binding specificity that is missing from Vitek and Solomon et al. WO 99/60024. If so, all pending claims remains distinguished for the other deficiencies in Vitek and Solomon noted above.

With respect to the additional ground for patentability of claims 98 and 100 arising from the recitation of an antibody that binds to an epitope within residues 1-7 of Aβ, applicants disagree that the binding specificity reported by Frenkel for an *in vitro* aggregation assay would have been thought to be relevant to a phagocytosis assay, as claimed. The epitope of Aβ responsible for aggregation is not necessarily the same as the epitope on amyloid deposits that would be required to bind an antibody and thereby induce phagocytosis *in vitro* or *in vivo*. For example, an epitope might promote aggregation between molecules of Aβ because of its charge characteristics. Conversely, an issue determining whether an epitope in amyloid deposits binds antibodies and thereby attracts phagocytic cells to digest the deposit might be surface accessibility. There was no reason to think that an epitopes for these different roles would be the same. Thus, assuming *arguendo*, Frenkel provides some indication of epitope specificity responsible for *in vitro* aggregation, there would be no reason to assume that a similar specificity was advantageous in a phagocytosis assay, as claimed.

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Amendment dated February 6, 2006

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-625-8100.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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